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Primer

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Developmental and epileptic encephalopathies

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Abstract

Developmental and epileptic encephalopathies, the most severe group of epilepsies, are characterized by seizures and frequent epileptiform activity associated with developmental slowing or regression. Onset typically occurs in infancy or childhood and includes many well-defined epilepsy syndromes. Patients have wide-ranging comorbidities including intellectual disability, psychiatric features, such as autism spectrum disorder and behavioural problems, movement and musculoskeletal disorders, gastrointestinal and sleep problems, together with an increased mortality rate. Problems change with age and patients require substantial support throughout life, placing a high psychosocial burden on parents, carers and the community. In many patients, the aetiology can be identified, and a genetic cause is found in >50% of patients using next-generation sequencing technologies. More than 900 genes have been identified as monogenic causes of developmental and epileptic encephalopathies and many cell components and processes have been implicated in their pathophysiology, including ion channels and transporters, synaptic proteins, cell signalling and metabolism and epigenetic regulation. Polygenic risk score analyses have shown that common variants also contribute to phenotypic variability. Holistic management, which encompasses antiseizure therapies and care for multimorbidities, is determined both by epilepsy syndrome and aetiology. Identification of the underlying aetiology enables the development of precision medicines to improve the long-term outcome of patients with these devastating diseases.

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Introduction

Developmental and epileptic encephalopathies (DEEs) are the most severe group of epilepsies, with seizure onset typically occurring in infancy or childhood. A DEE is a complex concept that incorporates two facets: a developmental encephalopathy, which usually leads to intellectual disability, coupled with an epileptic encephalopathy. The International League Against Epilepsy (ILAE) definition of an epileptic encephalopathy is that the epileptic activity itself contributes to severe cognitive and, sometimes, behavioural impairment, beyond what might be expected from the underlying pathology alone, and that these can worsen over time[1]. Most, but not all, patients with an epileptic encephalopathy have frequent seizures, often with multiple seizure types (Fig. 1). An essential feature of an epileptic encephalopathy is that there is slowing or regression in development, cognition or behaviour associated with frequent epileptiform activity on the electroencephalogram (EEG). Diagnosis of an epileptic encephalopathy is crucial because there may be therapeutic strategies that improve this epileptiform activity, thereby enabling the patient to make developmental gains.

In 2017, the ILAE expanded the concept of 'epileptic encephalopathy' to a 'developmental and epileptic encephalopathy', owing to a growing recognition that the aetiology of an epileptic encephalopathy, whether genetic, structural or otherwise, often causes developmental impairment in its own right[2]. Thus, the aetiology results in delayed development, either from birth or thereafter, before epileptiform activity appears on the EEG, as occurs in the prototypic DEE, Dravet syndrome. The epileptic encephalopathy is then superimposed on the developmental encephalopathy, further adversely affecting the child's development. By contrast, it is often impossible to separate the developmental encephalopathy from the epileptic encephalopathy aspects of a neonatal-onset DEE as both components affect the same period in development (Box 1). A DEE should be distinguished from a static developmental encephalopathy (typically resulting in intellectual disability) with epilepsy, in which the developmental encephalopathy alone (that is, not the epilepsy) causes developmental impairment[3].

The DEEs are classified according to epilepsy syndrome, defined as a distinctive cluster of clinical and EEG features, often associated with aetiological findings[4]; however, not all patients can be classified with a known syndrome (Fig. 2). One of the best examples is Lennox–Gastaut syndrome (LGS), defined in 1945 on the basis of tonic and atypical absence seizures, intellectual disability and slow spike-wave on EEG[5,6]. In 2022, LGS was defined by the ILAE for the first time, with the additional EEG feature of generalized paroxysmal fast activity in sleep[7]. LGS is highly aetiologically heterogeneous, with both acquired and genetic aetiologies, with or without a structural correlate. From an aetiological perspective, LGS mirrors the heterogeneous aetiologies of the DEEs more broadly.

In this Primer, we discuss the epidemiology, pathophysiological mechanisms, diagnosis and management of the DEEs. We review the effects of these devastating diseases on patients' quality of life and the tantalizing promise of precision medicine to improve outcomes.

Epidemiology

The considerable individual and societal impact of DEEs is best understood in the context of their epidemiology, which provides essential information to prioritize clinical, educational, social, financial and research resources[3,8–10]. Studies differ in recruitment methodology, epilepsy syndrome, aetiological classification, age range, cohort size and specific population, and whether they are prospective or retrospective. Despite these differences, consensus is emerging on the incidence and prevalence of the more common syndromes. DEEs typically present in childhood, before the age of 16 years, with a study from 2023 not identifying any presentations between 9 and 16 years[3]. DEEs are distinguished from epilepsies in adults and children with static intellectual disability, and epilepsies associated with progressive intellectual and neurological deterioration in which older patients of normal

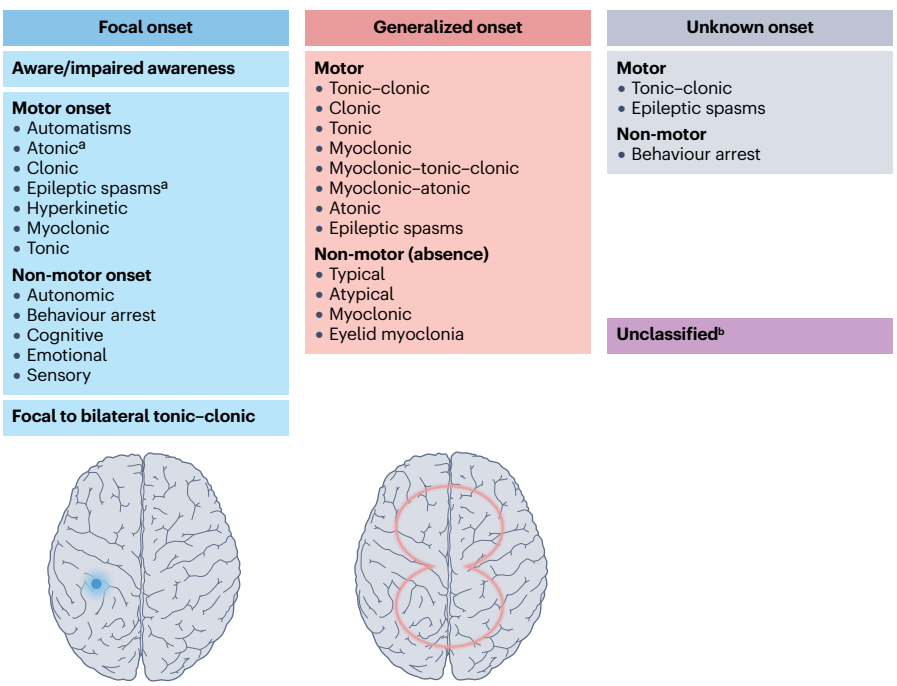

Fig. 1 | ILAE Classification of Seizure Types. Seizures are classified according to the 2017 International League Against Epilepsy (ILAE) Classification of Seizure Types. This formal revision of the international classification of seizure types in 2017 introduced updated terminology that has been adopted in clinical practice. [a]Degree of awareness for these seizure types is typically not specified as it is difficult to ascertain. [b]Due to inadequate information or inability to place in another category. Adapted with permission from ref. 163, Wiley.

intellect develop cognitive, neurological or psychiatric impairment due to the underlying aetiology, which may be associated with an epileptic encephalopathy (for example, progressive myoclonus epilepsies such as Lafora disease)[11].

In Wellington, New Zealand, the cumulative incidence of DEEs with onset up to age 16 years has been estimated at 169 (95% CI 144–199) in 100,000 or 1 in 590 children, based on EEG ascertainment[3]. Age-specific incidence varies through childhood with ~75% of cases beginning under 3 years of age, with a cumulative incidence estimated at 122 (95% CI 102–146) in 100,000 children in a retrospective study in Wellington[3]. In comparison, the estimated incidence of all epilepsies presenting under 3 years of age was 239 (95% CI 216–263) in 100,000 in a prospective study in Scotland, UK, with DEEs accounting for 86.1 (95% CI 72.7–101.3) in 100,000 children[9]. These studies differed in duration and size of birth cohort, but both used EEG records in their recruitment strategy.

Incidence estimates have been reported for many DEE syndromes; however, around one-third of patients cannot be classified as having a specific syndrome[3,9]. Table 1 lists the incidence estimates for the more common DEE syndromes; all studies were performed in high-resource settings. The global incidence of these syndromes is not known as access to the required specialized care and investigations is limited in resource-restricted settings. The most common DEE syndrome is infantile epileptic spasms syndrome (IESS) with an incidence ranging from 30.7 (95% CI 22.9–40.2) to 48.9 (95% CI 37.0–64.7) in 100,000 individuals; ~27% of IESS have a structural aetiology[3,9]. The most common structural aetiologies in people with DEEs can be divided into antenatal, perinatal or infantile acquired brain lesions and genetically determined malformations of cortical development (MCDs) (Box 2). IESS and LGS are defined by their seizure types and EEG features, and have multiple aetiologies, whereas Dravet syndrome is defined by electroclinical features, supported by a *SCN1A* pathogenic variant in 90% of cases[10,12]. In addition to enabling precision diagnosis, identifying the aetiology of DEE syndromes informs targeted management and genetic counselling, and underpins the development of precision therapies.

The aetiologies of DEEs vary around the world, with most studies undertaken in high-resource settings. Genetic studies currently identify the aetiology in ~50% of patients, including de novo, recessive, and X-linked pathogenic variants. The incidence of syndromes associated with de novo genetic variants is likely to be similar around the world[13], whereas, recessive causes occur more frequently in populations with high rates of consanguinity[14]. In resource-restricted regions, the incidence of acquired antenatal, perinatal and early infantile structural brain injury is increased[15,16].

Patients with a DEE have an increased mortality risk related to their seizures and comorbidities. The primary cause of death is sudden unexpected death in epilepsy (SUDEP)[17]; other causes include cerebral oedema following status epilepticus[18], chest infections and accidental causes[19]. The established mortality rate for Dravet syndrome among patients up to 20 years of age is 17%[20]. SUDEP rates for different genetic DEE syndromes have not been well defined, with the exception of Dravet syndrome, which has a Dravet-specific SUDEP rate of 4.4 (98% CI 2.3–7.8) in 1,000 person-years[19], accounting for most of the Dravet-specific mortality. Although cardiac dysfunction as evidenced by altered heart rate variability has been shown in Dravet syndrome, there is no definite evidence that the high SUDEP rate has a cardiac basis[21]. Different genetic DEEs vary considerably in their SUDEP risk, which is increased in DEEs due to sodium channelopathies[19]. Patients with a DEE with seizure onset in early infancy have an even higher mortality rate with 50% dying by age 2 years[7,8].

Box 1 | The relationship between seizures and developmental impairment in DEEs

The relationship between seizures and developmental impairment in developmental and epileptic encephalopathies (DEEs) is complex. The prominent role of genes implicated in DEEs in early brain development indicates a considerable contribution of aetiology to cognitive outcome, so developmental impairment (compounded by slowing or regression) is inherent to DEEs. However, several lines of evidence suggest that ongoing seizures and/or epileptiform activity worsen outcomes. In animal models, induced (non-genetic) seizures affect early brain development and network formation, resulting in cognitive impairment[250]. In humans, lack of a period of normal development in neonatal and infantile DEEs makes it difficult to determine any additive effect of seizures on cognitive outcome, but there are clear examples where improvement in seizure control or resolution of interictal electroencephalogram (EEG) abnormalities ameliorate cognitive outcome. For example, cessation of specific sodium channel blockers, which are contraindicated in Dravet syndrome, leads to improved seizure control and developmental gains in children and adults with Dravet syndrome[232]. In Landau–Kleffner syndrome, the onset of EEG abnormalities is associated with an acquired epileptic aphasia, and cognitive gains are often linked to improvement in the EEG abnormalities with appropriate treatment, although this is not always the case. Finally, in infantile epileptic spasms syndrome, a shorter time to spasm cessation is associated with improved developmental outcome in the group of children without a clear aetiology[251].

Mechanisms/pathophysiology

From the first identification of epilepsy genes (*CHRNA4*, *KCNQ2* and *SCN1B*) using family studies in the 1990s, genetic discoveries have shed light on disease mechanisms[22–25]. With >1,000 genes now implicated as monogenic causes of epilepsy in the Genes4Epilepsy database (http://github.com/bahlolab/genes4epilepsy)[26], the diverse functions of these genes highlight a vast array of biological processes that interact at cellular, organ and network levels. In this section, we discuss common disease mechanisms (Fig. 3 and Supplementary Table 1), with attention to inheritance patterns, loss or gain of protein function and phenotypic features, all of which underpin the development of precision therapies.

Channelopathies

Genes encoding voltage-gated or ligand-gated ion channels were the first genes identified in the pathophysiology of DEEs and remain the largest class today (Fig. 3a). They include voltage-gated sodium, potassium and calcium channels; γ-aminobutyric acid (GABA) receptor subunits; and ligand-gated glutamate (AMPA and NMDA) receptors. Genes encoding transporters of GABA, glutamate, glucose and ions are also implicated in DEE causation.

The most studied epilepsy gene is *SCN1A*, which encodes $Na_v1.1$, the α_1-subunit of the voltage-gated sodium channel (Supplementary Table 1). Loss-of-function (LOF) missense or truncating variants cause Dravet syndrome, the prototypic DEE[13,27], and also the non-DEE syndrome of genetic epilepsy with febrile seizures plus (GEFS+)[28]. *SCN1A* LOF particularly affects inhibitory interneurons, leading to impaired inhibition and epileptogenesis[29,30], with early ataxia and later crouch

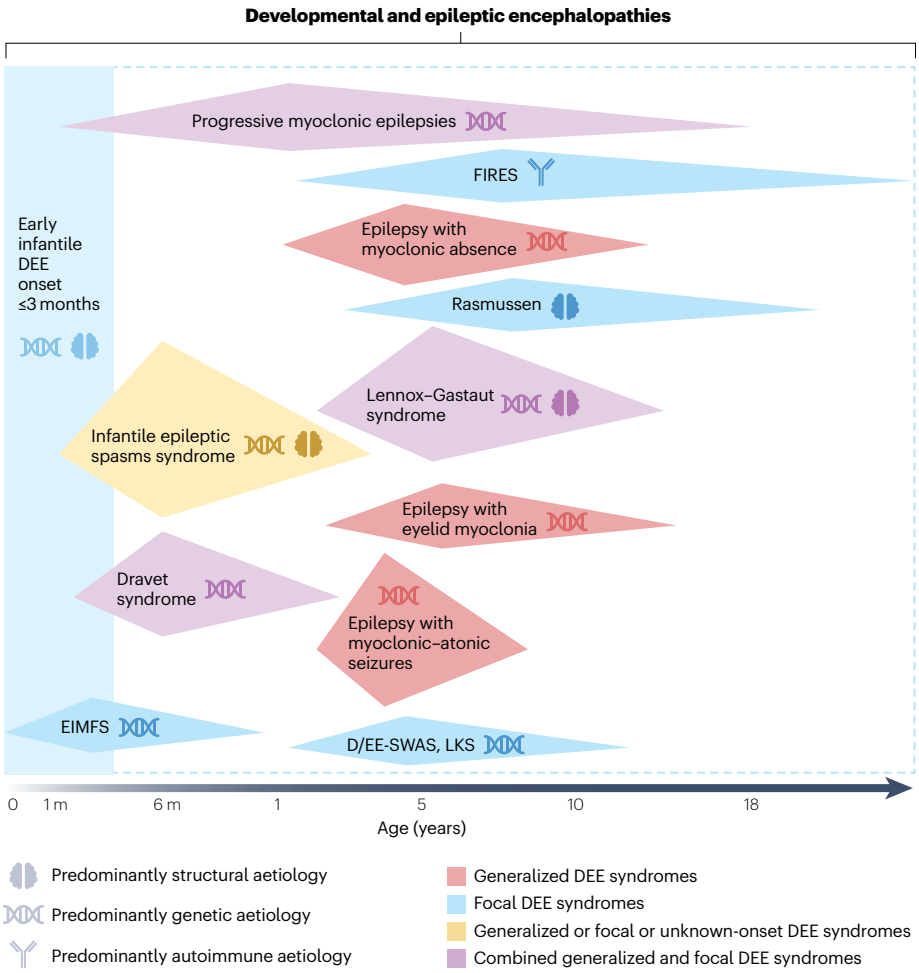

Fig. 2 | DEE epilepsy syndromes and their aetiologies. Multiple developmental and epileptic encephalopathy (DEE) epilepsy syndromes have been delineated but many individuals have a DEE that cannot be classified into a specific epilepsy syndrome. DEEs with onset by 3 months of age are classified as early infantile DEE. The range of ages and median ages (maximal height of diamond shape) at seizure onset differ between DEE epilepsy syndromes. The predominant aetiology of each syndrome also varies. D/EE-SWAS, developmental and/or epileptic encephalopathy with spike-wave activation in sleep; EIMFS, epilepsy of infancy with migrating focal seizures; FIRES, febrile infection-related epilepsy syndrome; LKS, Landau–Kleffner syndrome.

gait in Dravet syndrome that is probably due to involvement of cerebellar Purkinje neurons[31]. Recently, a new type of early infantile DEE (EIDEE) was identified that is caused by gain of function (GOF) *SCN1A* pathogenic variants with onset by 3 months of age[32,33]. In this profound *SCN1A* EIDEE, epileptic spasms, tonic seizures, hyperkinetic movement disorder and arthrogryposis may occur, in addition to the characteristic convulsive seizure types of Dravet syndrome, hemiclonic and tonic–clonic seizures. Understanding the functional consequences of the *SCN1A* pathogenic variant informs management, as some sodium channel blocker (SCB) antiseizure medications (ASMs) may exacerbate seizures in Dravet syndrome, whereas patients with the non-Dravet, EIDEE phenotype due to GOF variants may respond to SCBs, such as carbamazepine and phenytoin (Supplementary Table 1).

Pathogenic variants in *SCN2A*, *SCN8A* and *SCN3A*, each encoding a sodium channel α-subunit, cause DEEs with different phenotypes associated with GOF and LOF variants. Seizure onset under age 3 months in *SCN2A* DEEs and 6 months in *SCN8A* DEEs, is associated with GOF[34,35], and SCBs are efficacious in these phenotypes[34]. Some GOF and LOF variants also cause self-limited infantile-onset seizures, and it is critical to distinguish them from EIDEEs. Intriguingly, 75% of patients with *SCN3A* GOF variants have an MCD, such as polymicrogyria[36,37]. MCDs are disorders of disrupted brain development resulting in abnormal cortex formation including sulcation and gyration that can be focal or involve an entire hemisphere. MCDs may result in abnormal brain size and are due to a range of aetiologies including vascular, infectious, metabolic and genetic causes[38]. The association of *SCN3A* pathogenic variants with MCD[37], therefore, reflects a key role for sodium conductance in cortical progenitors, which affects cortical gyration during early brain development[39]. Taken together, genetic DEEs may cause structural changes, such as MCDs, highlighting that a genetic aetiology should be sought for MCDs which are often associated with a DEE[40,41].

Voltage-gated potassium channelopathies are an important cause of DEEs. LOF de novo *KCNQ2* variants cause neonatal-onset EIDEE[42], whereas inherited variants typically result in self-limited seizures[10]. *KCNQ2* EIDEE typically causes severe to profound impairment, despite seizures remitting in early life in >50% of patients[10,42]. Seizures often respond to SCBs[43]. Trials of precision therapy with KCNQ channel openers, such as retigabine or ezogabine, were complicated by aberrant skin and eye pigmentation in a small number of patients; modified compounds are in development[44–47]. Conversely, GOF *KCNQ2* DEEs include IESS associated with a recurrent GOF variant with severe outcome[48]. An intermediate non-DEE GOF group exists with mild to severe intellectual disability and seizures in some patients[49]. *KCNQ3* pathogenic variants are also a rare cause of DEE[50]. KCNQ3 and KCNQ2 form the heterotetrameric M-channel, which is important in

regulating neuronal excitability, with LOF, therefore, predisposing to epileptic seizures.

GOF and mixed GOF–LOF variants in *KCNA2*, which encodes the $K_v1.2$ channel subunit, are associated with DEEs[51]. The use of 4-aminopyridine, a K_v1 blocker, in patients with GOF variants improves seizures, ataxia, cognition and speech[52]. LOF variants in *KCNA1*, encoding the $K_v1.1$ channel subunit and typically associated with episodic ataxia type 1 (ref. 53), are rarely associated with DEEs[54,55].

Heterozygous de novo pathogenic variants in *KCNT1*, encoding a sodium-activated potassium channel, cause a spectrum of DEEs from epilepsy of infancy with migrating focal seizures (EIMFS) to sleep-related hypermotor epilepsy[56,57]. Functional studies show a range of GOFs due to increased potassium current amplitude, correlating with phenotypic severity[56,58]. There is cell type-specific vulnerability in inhibitory neurons, where GOF leads to decreased firing and, therefore, a loss of inhibition[59]. Initial hopes of precision therapy

Table 1 | Incidence estimates of developmental and epileptic encephalopathy syndromes

Epilepsy syndrome	Cumulative incidence per 100,000 live births (95% CI)	Methodology	Region and population size	Ref.
Early infantile developmental and epileptic encephalopathy (including Ohtahara syndrome and early myoclonic encephalopathy)	10 (5.8–16)	Prospective population-based, 3 years	Scotland; 169,500 live births	9
	Ohtahara syndrome 2.0 (0.5–7.9)	Retrospective population-based EEG and case record review period of 16 years	Wellington region, New Zealand; 108,861 live births	3
	Early myoclonic encephalopathy 2.0 (0.5–7.9)			
	Ohtahara syndrome 3.6 (1.8–7.2)	Retrospective population-based EEG and case record review period of 3 years	State of Victoria, Australia; 222,818 live births	8
	Early myoclonic encephalopathy 0.9 (0.23–3.6)			
KCNQ2 DEE	1.2 (0.14–4.3)	Prospective population-based, 3 years	Scotland; 169,500 live births	9
Epilepsy of infancy with migrating focal seizures	0.40 (CI not reported)	Surveillance study, 27 months	UK; members of British Paediatric Neurology Association	247
Infantile epileptic spasms syndrome	30.7 (22.9–40.2)	Prospective population-based, 3 years	Scotland; 169,500 live births	9
	48.9 (37.0–64.7)	Retrospective population-based EEG and case record review period of 16 years	Wellington region, New Zealand; 108,861 births	3
	32.6 (26–41)	Retrospective population-based EEG and case record review period of 3 years	State of Victoria, Australia; 222,818 births	8
	47.6 (34–69)	Retrospective epilepsy registry, EEG and medical record review period of 64 months	Northern Stockholm, Sweden; 69,333 births	248
Dravet syndrome	6.5 (3.2–10)	Prospective population-based, 3 years	Scotland; 169,500 live births	9
	5.1 (2.1–12.2)	Retrospective population-based EEG and case record review period of 16 years	Wellington region, New Zealand; 108,861 births	3
	6.4 (3.2–12.5)	Retrospective population-based EEG and case record review period of 42 months	Northern California, USA; 125,547 births	249
PCDH19 clustering epilepsy	4.85 (1.97–9.15); female births	Prospective population-based, 3 years	Scotland; 169,500 live births	9
	3.1 (1–9.5)	Retrospective population-based EEG and case record review period of 16 years	Wellington region, New Zealand; 108,861 births	3
CDKL5 DEE	2.36 (0.80–5.59)	Prospective population-based, 3 years	Scotland; 169,500 live births	9
SLC2A1 DEE	4.13 (1.07–7.19)	Prospective population-based, 3 years; epilepsy onset <3 years of age	Scotland; 169,500 live births	9
Gelastic seizures with hypothalamic hamartoma	2.0 (0.5–7.9)	Retrospective population-based EEG and case record review period of 16 years	Wellington region, New Zealand; 108,861 births	3
Lennox–Gastaut syndrome	13.2 (4.1–41.9)	Retrospective population-based EEG and case record review period of 16 years	Wellington region, New Zealand; 108,861 births	3
Epilepsy with myoclonic–atonic seizures	5.3 (2.4–10.1)	Prospective population-based, 3 years; epilepsy onset <3 years of age	Scotland; 169,500 live births	9
	16.64 (9.69–27.7)	Retrospective population-based EEG and case record review period of 16 years; epilepsy onset ≤16 years of age	Wellington region, New Zealand; 108,861 births	3
DEE with spike-wave activation in sleep and epileptic encephalopathy with spike-wave activation in sleep	12.8 (6.6–24.7)	Retrospective population-based EEG and case record review period of 16 years.	Wellington region, New Zealand; 108,861 births	3

DEE, developmental and epileptic encephalopathy; EEG, electroencephalogram.

Box 2 | Most frequent structural aetiologies in individuals with a DEE

Acquired structural aetiologies include:

- Infection
- Perinatal hypoxic–ischaemic encephalopathy
- Perinatal stroke
- Neonatal hypoglycaemia
- Traumatic brain injury

Genetic malformations of cortical development include:

- Lissencephaly–pachygyria–subcortical band heterotopia spectrum
- Focal cortical dysplasia
- Polymicrogyria
- Sturge–Weber syndrome

with quinidine, a non-specific potassium channel blocker, have not been fulfilled[60,61].

Calcium signalling is integral to key processes in early brain development, including synapse formation, neurotransmitter release, cell signalling and mitochondrial function. Pathogenic variants in voltage-gated calcium channel subunit genes cause DEEs. *CACNA1A* encodes $Ca_v1.1$, a subunit of the voltage-activated calcium channel intrinsic to synaptic neurotransmission. GOF variants cause DEEs with status epilepticus, alternating focal seizures, paroxysmal hemiplegia, neonatal jitteriness, ataxia and movement disorder[62,63]. LGS may occur with GOF and LOF *CACNA1A* variants[64,65]. Thus, it is difficult to predict functional effects based on phenotype, and functional characterization of variants or use of in silico tools is required[66]. GOF variants in *CACNA1E* and recessive LOF *CACNA1B* variants are associated with severe DEEs with dyskinesias[67,68].

Dysfunction of many GABA receptor subunit genes cause DEEs, as GABA is the principal inhibitory neurotransmitter in the brain. LOF variants in *GABRA1*, *GABRA2*, *GABRB2* and *GABRB3*, which encode $GABA_A$ subunits, lead to decreased neuronal inhibition resulting in many DEE phenotypes[64,69–72]. GOF and LOF *GABRB3* variants cause distinct DEE phenotypes with seizure onset under 6 months of age in those with GOF variants and after 1 year of age in those with LOF variants[73]. GOF phenotypes include hypersensitivity to vigabatrin, a GABA transaminase inhibitor that leads to increased GABA availability at the synapse, with functional testing showing increased receptor sensitivity[74]. GOF variants in *GABRB2* cause a severe DEE phenotype, with LOF variants leading to GEFS+ or later onset epilepsies[72]. GOF variants were also identified in *GABRD* which encodes an extrasynaptic GABA receptor subunit[75]. Fast inhibition in the brain is due to release of GABA onto postsynaptic $GABA_A$ receptors (phasic inhibition). However, disrupted tonic inhibition, a slower form of signalling due to activation of extrasynaptic $GABA_A$ receptors by GABA in the synaptic cleft, is emerging as a key disease process in DEE. Pathogenic variants in *SLC6A1* which encodes GABA transporter 1 (hGAT1), responsible for clearing GABA from the synaptic cleft, also lead to activation of extrasynaptic GABA receptors and increased tonic inhibition, resulting in epilepsy with myoclonic–atonic seizures[76]. 'Tonic GABA-pathy' has been suggested as the common disease mechanism underlying extrasynaptic GABA receptor DEEs[77]. An interesting corollary is seen in Angelman syndrome which results from *UBE3A* dysfunction, in which decreased GABA uptake results in reduced tonic inhibition leading to a myoclonic DEE with ataxia[78].

Ionotropic glutamate receptors are the major conduit of fast excitatory transmission in the brain and include NMDA and AMPA receptors. LOF and GOF variants in *GRIA2*, encoding the GluA2 subunit of the AMPA receptor, cause DEEs such as IESS[79]. NMDA receptors (NMDARs) are largely postsynaptic and co-activated by glutamate–glycine and depolarization of the postsynaptic membrane, enabling influx of calcium ions involved in regulation of processes key to encoding neuronal activity and, therefore, learning and memory[80]. Pathogenic variants in *GRIN1*, encoding GluN1, cause both dominant and recessive DEEs, highlighting the importance of considering both inheritance patterns when a variant of interest is identified. De novo heterozygous missense variants cause a neonatal DEE with a hyperkinetic movement disorder, stereotypies and oculogyric crises[64,81], whereas truncating heterozygous variants do not cause disease. Autosomal recessive null and missense variants lead to a more severe phenotype with increased mortality[81,82]. *GRIN1* variants cause a dominant-negative effect on other channel subunits[81]. Extensive diffuse polymicrogyria can be seen. Variants affecting GluN2B, encoded by *GRIN2B*, cause intellectual disability and/or autism spectrum disorder (ASD) in all patients with a range of DEEs, including IESS[83,84], and a hyperkinetic movement disorder. MCDs occur in some individuals with *GRIN2B* and *GRIN1* pathogenic variants[85], highlighting that NMDARs are involved in early brain development beyond neurotransmitter signalling. Functional characterization of *GRIN2B* variants shows complex effects[86]. Variants in *GRIN2D* cause infantile-onset DEE[87], whereas *GRIN2A* variants cause DEEs with onset from infancy to childhood, particularly developmental and/or epileptic encephalopathy with spike-wave activation in sleep (D/EE-SWAS)[83,88] and a speech disorder[88]. For GOF variants in *GRIN1*, *GRIN2A* and *GRIN2D*, there are limited reports of success using the precision medicine memantine, an NMDAR blocker[89]. For null variants in *GRIN2B* and *GRIN2A*, an *n*-of-1 trial (single-patient crossover study)[90] of L-serine, an essential amino acid which is a co-agonist of NMDARs, was effective for seizures in four of nine patients, but caused behavioural deterioration in a child with a GOF variant who was inadvertently treated[91,92]. A recent phase IIA trial of L-serine in 24 children with LOF *GRIN* variants showed substantial improvements in motor function and improved seizures in one patient[92].

Several ion or solute transporters have been implicated in DEEs. Heterozygous LOF variants in *SLC2A1* encoding GLUT1, the major glucose transporter at the blood–brain barrier, cause early-onset absence epilepsy, ataxia, epilepsy with myoclonic–atonic seizures and exercise-induced dyskinesia[93]. Others include Na^+,K^+-ATPase transporters (subunits encoded by *ATP1A2* and *ATP1A3*)[94], stretch-activated ion channels *TMEM63B*[95] and GABA transporter hGAT1 (*SLC6A1*), and EAAT2 glutamate transporter (*SLC1A2*)[96].

Understanding whether a variant in a gene encoding a subunit of an ion channel, receptor or transporter leads to LOF or GOF directs treatment selection, both with ASMs and emerging specific treatments, such as small molecules and antisense oligonucleotides. An overall GOF in an ion channel may, however, reflect several complex biophysical changes, such as altered voltage dependence of channel activation or inactivation, and changes in rates of fast or slow inactivation and rates of recovery from inactivation and channel opening probability. Moreover, the mechanisms of channel or receptor dysfunction are likely to be even more complex due to differing temporal, age-dependent, regional and cell-type dependent isoform expression patterns, effects of other subunit genes and acute and chronic compensatory changes

in other channels which may be helpful or harmful to brain function. For example, an antisense oligonucleotide which downregulates *SCN8A* ameliorates seizures and survival in mice with *Scn1a* or *Kcnq2* LOF, or *Scn8a* GOF variants[97].

Synaptopathies

There are more than 200 proteins in the synaptome[98], comprising presynaptic and postsynaptic membranes, synaptic vesicle machinery and associated supporting matrix and glial cell components, with many implicated in DEEs (Fig. 3b,c). The SNARE (soluble NSF attachment protein receptor) complex is responsible for synaptic vesicle formation, fusion and recycling, and neurotransmitter release into the synaptic cleft. 'SNAREopathies'[99] cause DEEs, often accompanied by movement disorders[100–104], due to pathogenic variants in genes including *STXBP1*, *SNAP2*, *VAMP2*, *DNM1* and *CPLX1*, disrupting the presynaptic complex (Supplementary Table 1). Autosomal recessive LOF variants in *TBC1D24*, encoding a GTPase-activating protein essential for synaptic vesicle trafficking[105], lead to DEEs with myoclonic seizures and EIMFS, with dystonia[106].

Disruption of the postsynaptic density, a massive assembly of cell adhesion molecules, scaffolding proteins, signalling molecules and cytoskeletal components at excitatory glutamatergic synapses, also results in DEEs. *SYNGAP1* encodes a major downstream component of the NMDAR signalling complex that interacts with small GTPases and other signalling proteins. SYNGAP1 influences synaptic transmission, AMPA receptor density and the morphology and plasticity of dendritic spines[107]. Pathogenic variants in *SYNGAP1* cause a generalized DEE with myoclonic–atonic seizures, absence with eyelid myoclonia, eating-induced reflex seizures and photosensitivity[108–110]. *IQSEC2*, a guanine nucleotide exchange factor that interacts with ARF6 and other GTPases, regulates AMPA receptor trafficking and, therefore, synaptic plasticity[111]. De novo pathogenic variants in *IQSEC2* are associated with DEEs; male individuals are more severely affected than female individuals[64,111,112].

Finally, several interacting synaptic adhesion and scaffolding molecules are implicated in DEEs. *CNTNAP2* encodes CASPR2, which forms a molecular bridge at synapses in addition to mediating neuronal migration. Biallelic variants result in a Pitt–Hopkins-like syndrome with early-onset epilepsy, hyperventilation, ASD, developmental delay and cortical dysplasia in some patients[113]. Disruptions of *NRXN1*, and rarely *NRXN2*, presynaptic neuronal adhesion proteins, cause DEEs including EIDEE[114]. The neurexins connect to synaptic organizers including gephyrin encoded by *GPHN*, the major scaffolding protein of postsynaptic glycinergic and GABAergic receptors. Heterozygous dominant-negative *GPHN* variants cause DEEs[115] and biallelic LOF variants are associated with EIMFS[116], confirming the role of gephyrin in maintaining inhibitory signalling in the brain. Collybistin is a brain-specific GDP–GTP-exchange factor encoded by *ARHGEF9*, which anchors gephyrin to the postsynaptic membrane in a tripartite interaction with neuroligin cell adhesion molecules (and binds directly to the α_3-subunit of $GABA_A$), forming a lattice to scaffold glycine and $GABA_A$ receptors[117]. Other synaptic genes associated with DEEs include *TANC2* (ref. 118), *SHANK3* (refs. 119,120) and *ADAM22* (ref. 121).

Cell signalling

Several cell signalling pathways have been implicated in epilepsies, with the most prominent being the mechanistic (formerly mammalian) target of rapamycin (mTOR) pathway[122,123] (Fig. 3d). The mTOR signalling pathway regulates fundamental processes including cell metabolism, growth, proliferation and survival. Both germline and somatic mosaic pathogenic variants in most genes encoding components of the canonical mTOR signalling ('mTORopathies') and amino acid-sensing ('GATORopathies') pathways are associated with focal epilepsies. These may occur as germline variants, somatic variants limited to dysplastic brain, or a combination of a germline variant with a brain somatic mosaic variant within dysplastic tissue representing a 'second hit'[124]. Germline variants in *TSC1* and *TSC2* cause tuberous sclerosis complex (TSC), a complex multisystem disorder affecting the brain, skin, kidneys, heart, lungs and eyes. Neurodevelopmental disorders and epilepsy are common, 88% of patients have epilepsy and 40% have IESS[125]. MRI reveals cortical tubers, in which a second somatic mosaic variant may be identified. Vigabatrin is the first-line treatment for IESS associated with TSC, and mTOR inhibitors are considered after failure of two appropriate ASMs[126]. Germline variants in *PTEN* cause ASD and macrocephaly with epilepsy, whereas variants in *AKT3* and *PIK3CA* cause megalencephaly. Germline LOF variants in proteins that comprise the GATOR1 complex (*DEPDC5*, *NPRL2* and *NPRL3*), responsible for sensing amino acid levels, cause both non-lesional focal epilepsy and epilepsy associated with focal cortical dysplasia (FCD)[122]. *DEPDC5* pathogenic variants were first reported in familial focal epilepsy with variable foci[127,128], and later associated with DEEs[129]. Studies employing deep targeted sequencing in resected brain tissue have highlighted the role of brain-restricted somatic mosaic variants in nearly all of these genes in FCD type II, sometimes with hemimegalencephaly[123], with variant allele frequencies as low as 0.01%[130]. mTOR pathway inhibitors, including everolimus and sirolimus, may be beneficial as a targeted treatment[131].

G protein signalling is another ubiquitous cell signalling pathway relevant to DEEs. Heterotrimeric G proteins transmit signal from transmembrane G protein-coupled receptors (GPCRs) at the cell surface affecting many cellular processes. GPCRs that are important in epilepsy include NMDA and AMPA receptors. De novo variants in *GNAO1*, *GNB1* and *GNAI1* are important causes of DEEs. *GNAO1* and *GNAI1* encode α-subunits of the G protein complex, and both inhibit adenylate cyclase to reduce cAMP levels. Biochemical studies of *GNAO1* pathogenic variants causing DEE show loss of cAMP inhibition. By contrast, *GNAO1* GOF variants cause an early-onset movement disorder with or without epilepsy[132]. De novo pathogenic variants in *GNAI1* in a series of 24 individuals caused developmental delay, substantial speech impairment and seizures in 75% of individuals[133]. Missense variants affect the GDP-binding domain, but the functional effects of the variants (LOF versus GOF) have not yet been elucidated. *GNB1* encodes a β-subunit of the G protein complex; pathogenic variants disrupt protein–protein interactions between α-subunits and βγ-subunits[134].

Epigenetic regulation

Genes that encode parts of the epigenetic machinery, such as transcription factors, chromatin remodellers and histone modifiers, have been implicated in DEEs[135] (Fig. 3e). Key genes include *MECP2*, a ubiquitously expressed methyl-CpG binding protein, for which LOF leads to Rett syndrome in girls and duplication typically leads to DEE with profound impairment in boys[136]. *ARX*, which encodes a homeodomain transcription factor, results in a phenotypic spectrum with LOF variants early in the gene causing MCDs, including lissencephaly, and repeat expansions leading to IESS, often associated with a severe hyperkinetic movement disorder. *CHD2*, encoding a chromodomain helicase binding protein[108], causes photosensitive myoclonic DEEs including epilepsy with eyelid myoclonia and epilepsy with myoclonic–atonic seizures[137]. *EEF1A2*, encoding a translation elongation factor[138], is associated with

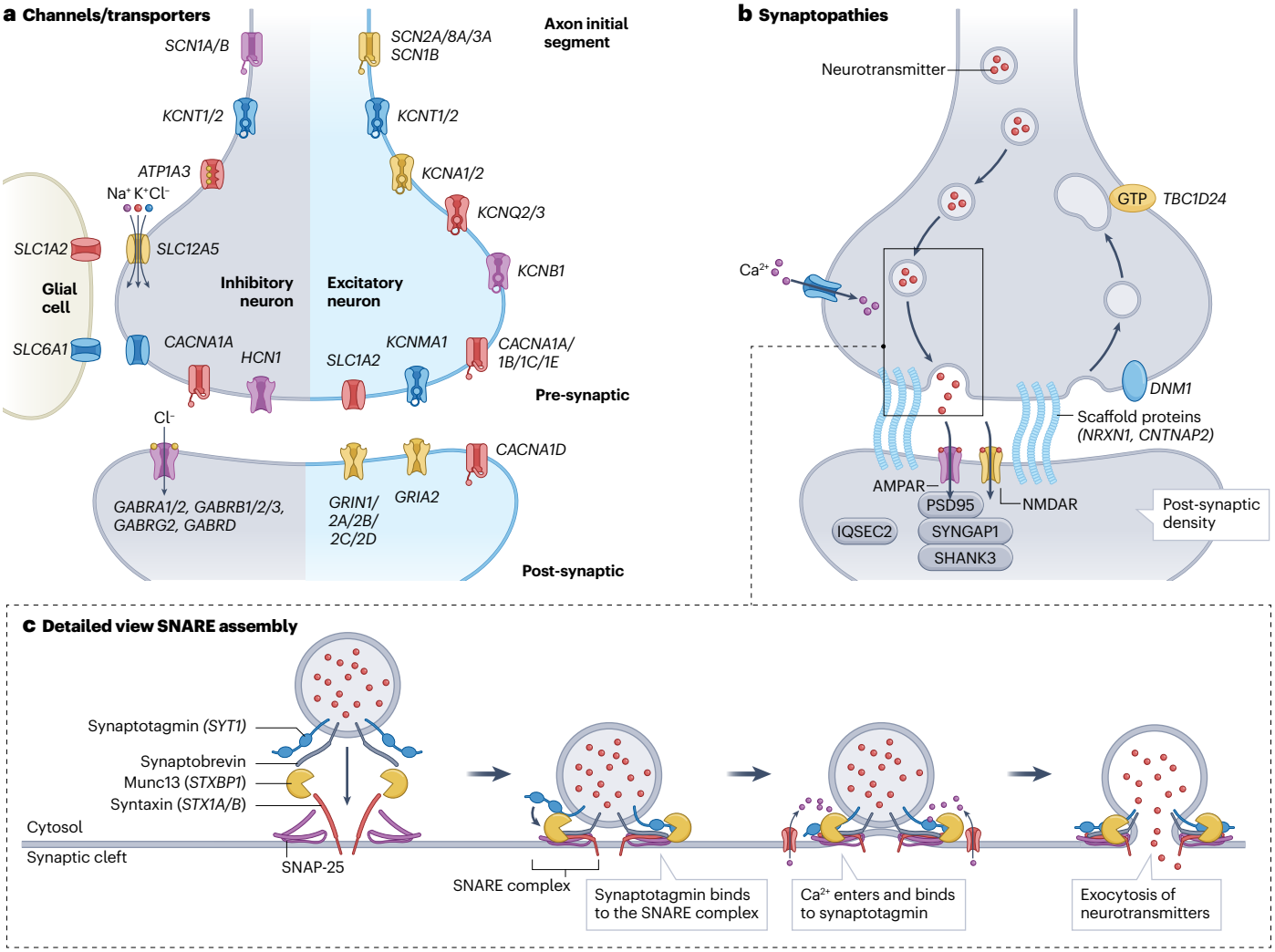
a Channels/transporters
SCN1A/B
KCNT1/2
ATP1A3
Na+ K+Cl-
SLC1A2
SLC12A5
Glial cell
Inhibitory neuron
SLC6A1
CACNA1A
HCN1
Cl-
GABRA1/2, GABRB1/2/3, GABRG2, GABRD
Axon initial segment
SCN2A/8A/3A SCN1B
KCNT1/2
KCNA1/2
KCNQ2/3
KCNB1
Excitatory neuron
KCNMA1
SLC1A2
CACNA1A/ 1B/1C/1E
Pre-synaptic
CACNA1D
GRIN1/ 2A/2B/ 2C/2D
GRIA2
Post-synaptic
b Synaptopathies
Neurotransmitter
GTP
TBC1D24
Ca2+
DNM1
Scaffold proteins (NRXN1, CNTNAP2)
AMPAR
NMDAR
PSD95
IQSEC2
SYNGAP1
SHANK3
Post-synaptic density
c Detailed view SNARE assembly
Synaptotagmin (SYT1)
Synaptobrevin
Munc13 (STXBP1)
Syntaxin (STX1A/B)
Cytosol
Synaptic cleft
SNAP-25
SNARE complex
Synaptotagmin binds to the SNARE complex
Ca2+ enters and binds to synaptotagmin
Exocytosis of neurotransmitters
d Cell signalling and metabolism
mTOR pathway
Growth factor receptor
GATOR1 complex
DEPDC5
NPRL2
NPRL3
PI3K
PTEN
PIP2
PIP3
AKT
Rag A/B
Rag C/D
TSC1/2
Rheb
MTORC1
Cell growth and proliferation
G protein receptor signalling
Neurotransmitter
Receptor
Ca2+
GNB1
GNA01
γ
GTP
GDP
Inhibition of calcium channels
Altered cAMP signalling
Reduced neurotransmitter release
Protein modification
Ub
Ubiquitination KLHL20
UFM1
UFMylation UBA5
e Epigenetic regulation
Chromatin modification: CHD2
Histone modification: SETD1B
RNA polymerase
RNA
Promoter
Transcription factors
Enhancer
Cis-regulatory elements
Transcription activation: MECP2, ARX, PURA
Transcription elongation: EEF1A2

Fig. 3 | Biological mechanisms implicated in DEEs. A wide range of biological processes are perturbed in developmental and epileptic encephalopathies (DEEs). **a**, Dysfunction of sodium, potassium and calcium channels and ion and solute transporters results in DEEs. **b**,**c**, Synaptopathies (part **b**) include disruption of the soluble *N*-ethylmaleimide-sensitive factor activating protein receptor (SNARE) machinery responsible for synaptic vesicle formation and release, synaptic scaffold proteins, postsynaptic receptors and signalling cascades (part **c**). **d**, A number of genes in key cellular processes including the mammalian/mechanistic target of rapamycin (mTOR) pathway and G protein receptor signalling lead to DEEs. **e**, Epigenetic regulation including chromatin modification and transcription modification are also major causes of DEEs. Excitatory neurons are represented in blue, inhibitory neurons in grey and glial cells in light brown. Ub, ubiquitin; UFM1, ubiquitin-fold modifier 1.

IESS. *PURA*, is involved in transcriptional regulation[139], and pathogenic variants cause severe myoclonic DEE with respiratory insufficiency and hypotonia[140]. *SETD1B*, a histone methyltransferase[141], causes a multisystem disorder with obesity and epilepsy with eyelid myoclonia. In each case, haploinsufficiency of the protein results from de novo dominant LOF variants. Genes involved in epigenetic regulation of gene expression are ubiquitously expressed; yet, phenotypes resulting from haploinsufficiency are largely restricted to the brain. Deciphering tissue-specific functions and downstream targets may shed light on disease mechanisms.

Epigenetic methylation studies are unlocking the aetiology in patients with unsolved DEEs. A recent study of methylation profiles in 582 unsolved patients identified the aetiology in 2% of individuals[142] (a similar yield to that observed when performing genome sequencing after exome sequencing). Episignatures can reveal abnormal patterns suggestive of specific genes[143], highlighting the need for further sequencing to identify intronic or previously missed variants or structural molecular anomalies.

Cell metabolism

The clinical phenotype of many classic metabolic disorders includes epilepsy. This section describes recently identified genetic causes of DEEs that affect cellular metabolism or related processes. *UBA5* encodes an E1-activating enzyme, the initial enzyme that is required for a process called UFMylation, a ubiquitin-like post-translational modification of proteins. Biallelic pathogenic variants in *UBA5* cause DEEs, severe developmental impairment, hypotonia, spasticity, microcephaly and growth failure[144]. Nearly all affected individuals have one LOF allele and one hypomorphic allele that retains some enzymatic activity, suggesting that complete loss of *UBA5* is lethal.

De novo dominant mutations in *KLHL20* have been identified[145]; KLHL20 protein is part of a complex that mediates ubiquitination, a process also implicated in Angelman syndrome due to variants involving *UBE3A*. *WWOX* encodes a ubiquitously expressed WW domain-containing oxidoreductase that is involved in cell growth and differentiation and was originally identified as a tumour suppressor. Recessive variants cause a spectrum of phenotypes including DEE with microcephaly and profound delay and spinocerebellar ataxia[146].

CLN2 disease causes the recessive neurodegenerative late-infantile form of neuronal ceroid lipofuscinosis, or late-infantile Batten disease[147]. Onset of focal seizures or myoclonic–atonic seizures occurs at 2–4 years of age in a child with normal development or isolated language delay. It is followed by rapid progression to a progressive myoclonus epilepsy, severe regression, visual failure and early death. Precision therapy using intracerebroventricular enzyme replacement with recombinant human tripeptidyl peptidase 1 slowed disease progression in one study[148].

As with epigenetic regulators, dissecting cell-type-specific effects or functions may shed light on how disruption of these ubiquitous processes results in largely brain-restricted disorders.

Diagnosis, screening and prevention

Diagnosis of an epileptic encephalopathy is based on the child showing developmental slowing or regression in association with frequent epileptiform activity on EEG[1]. Developmental slowing or regression can be challenging to identify, especially in children with pre-existing developmental delay. Listening carefully to parental concerns is crucial, as they are the best placed to identify a subtle change in their child's abilities, particularly in those with preceding impairment, such as a reduction in eye contact or social interaction. Similarly, when a child with normal development develops an epileptic encephalopathy, slowing in development can be hard to identify. For example, children with Landau–Kleffner syndrome may present with behavioural problems due to their auditory agnosia during which they cannot comprehend common sounds in their environment[7,149]. For specific DEE syndromes, appropriate management may facilitate a good outcome with the child ultimately being of normal intellect, as is common in the epileptic encephalopathy of epilepsy with myoclonic–atonic seizures[7,150]. A DEE can be distinguished from an epileptic encephalopathy as a pure epileptic encephalopathy occurs in the context of normal development before either seizure onset or development of frequent epileptiform activity on EEG. Such a distinction is, however, often impossible in an infant under 3 months of age who presents with developmental impairment and an epileptic encephalopathy, such as EIDEE, including Ohtahara syndrome and early myoclonic encephalopathy[10] (Box 1).

As a group, DEEs are far more complex diseases than just seizure disorders. They are multimorbidity diseases typically affecting a range of systems. They often include motor dysfunction such as cerebral palsy[42], movement disorders[151] and gait decline[31], psychiatric features such as ASD[110], behavioural problems[152], mood disorders, psychosis[153], and speech[154], sleep[155], respiratory and gastrointestinal problems. As the child grows, many of these morbidities, such as behaviour, become the main concern for families who are already skilled at managing seizures[156]. Holistic clinical care requires consideration of the entire gamut of morbidities that a child or adult with a DEE faces.

DEEs have historically been diagnosed on the basis of their electroclinical presentation[1]. It typically takes time for the full syndromic picture to emerge, during which the child often shows developmental slowing or regression. Diagnosis of a DEE can now be made far earlier with increasing recognition of the initial presentation together with prompt access to molecular diagnosis in clinical practice, often even before the EEG shows epileptiform activity and developmental slowing occurs. Indeed, a recent study involving rapid genome sequencing (median time from seizure onset to sequencing result of 37 days) in infants with seizures beginning under 1 year of age, identified the genetic aetiology in 46% of 100 children, with clinical utility in 56%, prognostic counselling in 86% and genetic counselling implications in all those with a pathogenic variant[157]. Access to genetic testing means that infants with Dravet syndrome are diagnosed as early as their initial presentation. As one-third of patients present with febrile status epilepticus, either a hemiclonic or generalized tonic–clonic seizure

(GTCS), the diagnosis of Dravet syndrome may be considered from age 6 months when development and the EEG are typically normal[12,158]. This enables early targeted treatment with the most appropriate ASMs to control life-threatening seizures to ameliorate the adverse developmental consequences of frequent seizures and status epilepticus. Observational studies have suggested that appropriate therapies improve developmental outcomes, but long-term outcome is rarely normal and a multimorbidity picture remains usual[27]. Early diagnosis also helps to avoid contraindicated ASMs that exacerbate seizures in specific DEEs. A still common example is the use of SCBs, carbamazepine or oxcarbazepine, in infants with hemiclonic or tonic–clonic seizures who have undiagnosed Dravet syndrome, as these specific ASMs commonly cause seizure exacerbation with adverse developmental consequences[159].

Of note, a serious diagnosis, such as a DEE, in infancy carries considerable consequences that require proactive clinical management. From diagnosis, families experience considerable grief and need intense support as the disease evolves[160,161]. With the accessibility of the internet and social media, families are faced with far more information than ever before, which is both empowering and daunting, as the future may appear bleak with so many issues that could develop. The treating clinician should, therefore, provide holistic care, ideally supported by a multidisciplinary team, including nurses trained specifically in managing patients with a DEE. They need to guide families to the appropriate specialist for management of new problems as they emerge and ensure that therapies and education are targeted to the child's level of function.

Epilepsy syndromes

DEEs include a wide range of epilepsy syndromes, defined by their electroclinical features and, in some cases, imaging findings[4,7,10,11,162] (Fig. 2). Epilepsy syndromes are defined by their age at onset, seizure types[163], EEG features, developmental course and associated features. Diagnosis of a DEE syndrome informs aetiological investigations, prognostic and genetic counselling, and selection of therapeutic approaches. The aetiology of DEEs is frequently genetic, and may be associated with normal imaging, diffuse or focal structural abnormalities such as MCD[164,165] and, less commonly, metabolic features. Acquired causes, such as ischaemic injury, infection and hypoglycaemia, are a small but important group[166]. For some of the rarer syndromes, such as Rasmussen syndrome and febrile infection-related epilepsy syndrome, the aetiology is currently unknown.

With the rapid advances in next-generation sequencing, 50% of patients with a DEE have a pathogenic variant of major effect identified[167]. Current analyses of monogenic epilepsy genes have implicated >900 genes in DEEs (Gene4Epilepsy; http://github.com/bahlolab/genes4epilepsy) out of >1,000 established monogenic genes[26]. Genetic DEEs are most commonly regarded as de novo dominant disorders; however, more DEE genes follow autosomal recessive than dominant inheritance, with a small number following X-linked or mitochondrial inheritance patterns[26]. The percentage of patients who have a causative variant identified varies markedly across different DEE syndromes. For example, Dravet syndrome is relatively genetically homogeneous with >90% of patients having a pathogenic variant in *SCN1A*[12], whereas EIMFS is highly genetically heterogeneous with >30 genes implicated and 70% of those affected having a pathogenic variant of major effect identified. The genes that cause EIMFS may follow autosomal dominant, X-linked and autosomal recessive inheritance, so an understanding of how each gene is inherited is essential when providing accurate diagnostic and genetic counselling for families[168]. Genetic DEEs implicating a range of disease mechanisms may also be associated with structural changes in the brain, such as MCD, that probably result from changes in gene expression during early brain development. These findings reinforce the need to consider a genetic aetiology for all structural changes in the brain.

One should aim to identify both the DEE epilepsy syndrome diagnosis *and* the aetiology in each patient, as they provide complementary information that critically inform patient management. Knowing the gene is not sufficient, as each gene is typically associated with a spectrum of phenotypes. For example, pathogenic variants in the sodium channel subunit genes, *SCN1A*, *SCN2A* and *SCN8A*, cause DEEs and self-limited epilepsies, which require very different treatment approaches[10]. Furthermore, a gene can be associated with different DEE syndromes that reflect GOF or LOF and, therefore, need therapies with the mode of action tailored to the underlying dysfunction. *SCN1A* again provides a good example, with Dravet syndrome arising due to LOF pathogenic variants[169], and GOF pathogenic variants causing a profound EIDEE with an expanded phenotypic spectrum[32,33].

Despite the epilepsy syndrome informing diagnosis, aetiology and management, many patients with a DEE or an epileptic encephalopathy do not fit neatly into a recognized epilepsy syndrome diagnosis. They do, however, share the increased risk of comorbidities and SUDEP that occur in DEE syndromes; thus, recognizing the severe nature of their disease is crucial.

Investigations

All patients with a DEE require investigations to characterize their epilepsy and identify an underlying aetiology[166]. Video-EEG studies, often beginning with a routine EEG incorporating hyperventilation and intermittent photic stimulation, are required. Both hyperventilation and intermittent photic stimulation increase the likelihood of eliciting epileptiform activity (such as generalized spike-wave) and sometimes seizures (typically absence seizures if hyperventilation is well performed, which is often not possible in these patients). Detailed characterization with video-EEG studies of ictal episodes often adds useful information. Epileptic and non-epileptic seizures and movement disorders can be distinguished[151], providing vital information in guiding patient management. Often, an EEG during sleep provides additional findings that guide epilepsy syndrome classification (such as generalized paroxysmal fast activity in LGS and spike-wave activation in sleep in the syndromes of epileptic encephalopathy with spike-wave activation in sleep (EE-SWAS) and developmental and epileptic encephalopathy with spike-wave activation in sleep (DEE-SWAS), directing therapy selection[170].

All patients should have brain MRI, ideally with a 3 T machine using epilepsy sequences, to exclude a congenital or acquired structural lesion, such as an MCD or an ischaemic insult. If there is evidence of a unifocal lesion that could be driving an epileptic encephalopathy network, presurgical evaluation is indicated (Fig. 4). Further studies such as SPECT (ictal compared with interictal), fluorodeoxyglucose PET, and, in some individuals, more sophisticated imaging, such as functional MRI studies, may be useful, but may be challenging to perform. Overall, relatively few patients with a DEE are candidates for epilepsy surgery but, if a unifocal resectable lesion is identified, such as a FCD, successful surgery can be transformational[166,171]. In an epidemiological study of severe epilepsies beginning before 18 months of age, which excluded patients with Dravet syndrome for methodological reasons, the aetiology was determined in 67% of patients (76/114). Specifically, a genetic or presumed genetic basis was identified in 62 patients (54%): 14 with

FCD, 17 with other brain malformations, six with a metabolic disorder, nine with chromosomal disorders, 16 with a single gene disorder, and 14 with acquired brain lesions[8,166]. MCD, including FCD, may be associated with a pathogenic germline or somatic variant, which may show a mutation gradient in resected brain tissue. In some individuals, a second genetic hit with a combination of both somatic and germline mutations in the same gene or genes in related pathways (for example, the mTOR pathway) is identified[124].

Neuropsychological evaluation is invaluable in characterizing a patient's cognition, together with negative or positive changes over time, and responses to specific therapies. Cognitive decline may indicate the need for sleep EEG studies to identify a so-far unrecognized epileptic encephalopathy, such as DEE-SWAS or EE-SWAS[170].

Routine genetic testing often begins with a chromosomal microarray as causative copy number variants (CNVs) are identified in at least 4% of patients with a DEE[172]. Contributory pathogenic CNVs occur in another 4%, in whom the CNV contributes to, but is not wholly causative of, the underlying aetiology[172]. New chromosomal microarrays with increased density detect smaller CNVs not visible previously. Mosaic pathogenic CNVs are increasingly identified, with a greater yield from salivary DNA than from blood-derived DNA, as salivary epithelial cells are embryologically closer to neural cells, deriving from ectoderm, than lymphocytes[173]. Importantly, ring chromosomes may be missed by chromosomal microarray and require a classical karyotype for detection; detection of low levels of mosaic rings can be challenging and warrants discussion with the laboratory.

Next-generation sequencing has transformed our understanding of the aetiologies of the DEEs, enabling identification of their cause in 50% of patients[166,167]. Testing is moving from exome sequencing, analysing the 1–2% of the genome that encodes proteins (exons) and in which most pathogenic variants are found, to genome sequencing[63,157]. Gene panels have been extensively used but only capture a subset of all >900 DEE genes, thereby failing to identify causative variants in genes that have not been sequenced[26]. Some gene panels use exome sequencing, but analysis is limited to genes included in the panel; in such instances, re-interrogation for genes that have not been analysed should be requested. However, the genetic landscape constantly evolves owing to the discovery of new genes, so exome sequencing is now recommended where feasible[174]. Genome sequencing, now moving into clinical practice, enables analysis of intronic and regulatory regions. A 2023 genome analysis of infants with seizures beginning in the first year of life identified a genetic cause in 43% of 100 infants, and all had implications for disease management[157].

Mosaicism is increasingly recognized as an important cause of DEEs, including germline and somatic (tissue-limited) mosaicism. Detection of low-level germline mosaicism in blood-derived DNA requires high-depth sequencing or specialized techniques, such as droplet digital PCR[175]. Sometimes, lower mosaicism levels are associated with milder disease[12,175,176]. Somatic mosaicism can be found in brain-derived DNA at low levels inn surgical specimens, cerebrospinal fluid or implanted EEG electrodes[122,177,178].

Epigenetic analysis is beginning to shed light on other types of pathogenic changes. Episignatures, derived from disruption in genome-wide DNA methylation profiles, are recognized for many genes resulting in neurodevelopmental disorders including ASD, with some relevant to DEEs[143]. As genomic DEE episignatures are identified, testing may clarify the pathogenicity of variants of unknown significance and identify other pathogenic variants with imprinting and repeat expansion disorders[142,179].

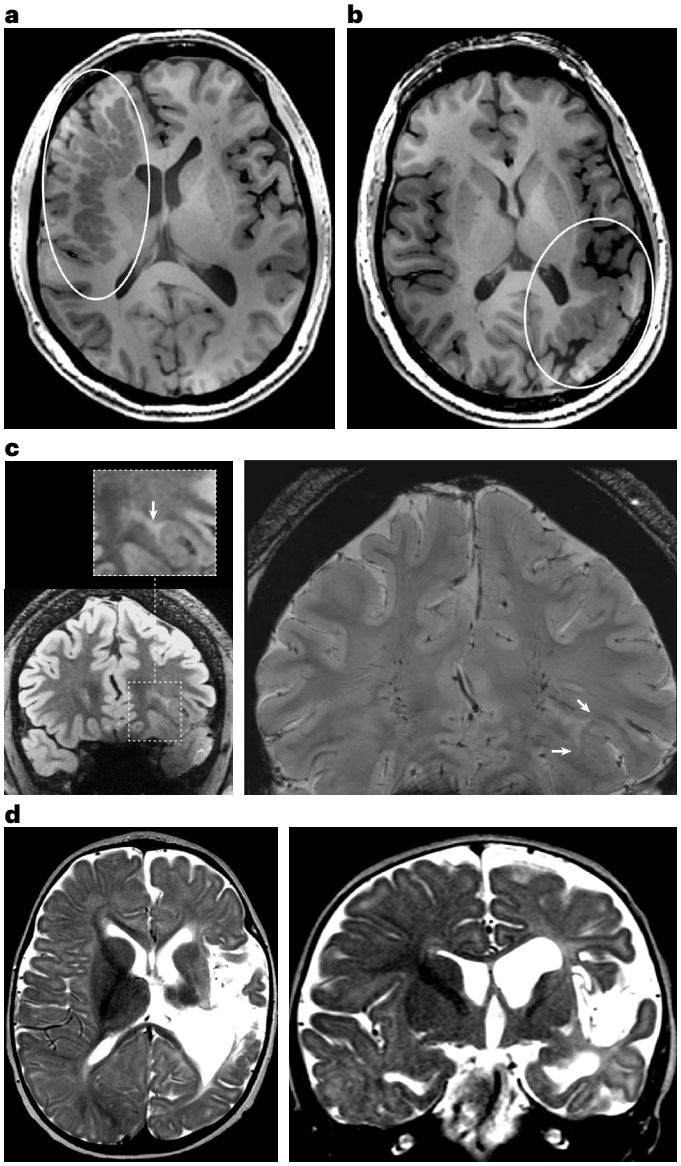

Fig. 4 | Examples of structural aetiologies of developmental and epileptic encephalopathies. a, 7 T MRI scan in a young patient with focal epilepsy shows extensive subcortical heterotopia in the right anterior quadrant. **b**, 7 T MRI scan in a young patient with focal epilepsy shows polymicrogyria involving the left posterior quadrant. **c**, 7 T MRI scan in patient with focal cortical dysplasia and focal epilepsy shows thickening of the cortex surrounding the depth of a sulcus and high signal intensity of the underlying white matter (arrow). This anatomic location of the dysplasia is called 'bottom of the sulcus dysplasia' and the white matter abnormality is called a 'transmantle sign'. **d**, Left hemispheric porencephaly in a patient with focal epilepsy.

Routine blood and urine tests should be performed early in a child's presentation, including specific testing tailored to the patient's presentation[166]. These include blood creatinine, ammonia, amino acids, acylcarnitines, biotinidase, uric acid, recurrent mitochondrial pathogenic variants, *POLG* common pathogenic variants, transferrin isoforms, copper, caeruloplasmin, very long-chain fatty acids, white

cell enzymes, glucose, lactate, pyruvate and amino acids. Urine testing includes organic acids, amino acids, piperideine-6-carboxylate, *S*-sulfocysteine, guanidinoacetic acid, purines and pyrimidines. Cerebrospinal fluid tests should be considered including cell count, protein, glucose, lactate, pyruvate, amino acids and neurotransmitters. Testing should focus on treatable conditions, such as vitamin-responsive epilepsies[180]. The full gamut of investigations is often not available in low-income and middle-income settings, where access may be limited to EEG and imaging studies, and a genetic aetiology cannot be identified due to lack of availability of genetic testing.

Reproductive counselling

In any patient with a genetic DEE, reproductive counselling is essential. In patients thought to have a de novo pathogenic variant, high-depth sequencing of parental blood or salivary samples found that 8% of patients had a parent with low-level mosaicism[175]. Parents with mosaic levels of <13% were unaffected and those with higher levels had febrile seizures or epilepsy. Parental mosaicism places parents at an increased risk of having a second child with a DEE, as a small population of their sperm or ova carry the pathogenic variant. Testing of blood or saliva would not detect mosaicism limited to gonads, so genetic counselling should always discuss this possibility and potential testing of a subsequent pregnancy should be considered (for example, with IVF, chorionic villus sampling or amniocentesis). If patients with genetic DEEs wish to have children, the recurrence risk also needs to be carefully discussed.

Management

Management of the DEEs requires a focus on both seizure control and comorbidities. A holistic approach involves a multidisciplinary team to provide appropriate therapies to mitigate developmental, psychiatric and behavioural challenges.

Reducing seizure burden

In the epilepsies, ASMs have historically been selected to treat seizure type, rather than epilepsy syndrome, beginning with empirical trials of standard ASMs appropriate to the patient's presenting seizure type, such as carbamazepine for focal, valproate for generalized, and broad spectrum ASMs (such as valproate, levetiracetam and lamotrigine) for combined focal and generalized seizure types. For DEEs, seizures are usually drug-resistant, with many ASMs being tried in patients in an effort to control seizures. This approach can be particularly problematic for DEEs, in which a lack of diagnosis of the epilepsy syndrome may result in inappropriate prescription of an ASM that causes seizure exacerbation with potential adverse developmental consequences[159].

Until now, ASM treatment choices for DEEs were made largely on the same general principles of targeting the seizure types mentioned above; however, seizures in DEEs are typically drug-resistant. There are ASM protocols published for specific DEE syndromes based on expert consensus[181,182]. Even when an aetiological genetic diagnosis is made, meaningful change in the treatment paradigm has not yet been possible for most DEEs[183]. In a 2021 observational study in 293 patients with genetic epilepsies, treatment changes were undertaken because of the genetic findings in 32%, including rational precision medicine treatment or a treatment change prompted by the genetic diagnosis, but not directly related to known pathophysiological mechanisms[183]. By contrast, a 2023 genome sequencing study of infants presenting with seizures under 1 year of age identified the causal variant in 43% with immediate treatment implications in 56%, informing additional evaluation in 65% and prognostic counselling in 86%[157].

Nonetheless, we are at an inflexion point in DEE management as precision therapy should be considered from the day a genetic diagnosis is made. Traditional ASMs can be used as precision therapies when the functional effect of the pathogenic variant is understood (Supplementary Table 1). SCBs, particularly carbamazepine and phenytoin, are efficacious in GOF DEEs due to pathogenic variants in sodium channel genes (*SCN1A*[33], *SCN2A*[184] and *SCN8A*[185]) and potassium channel genes (*KCNQ2* (ref. 43)). Trials targeting specific channelopathies are being developed: potent selective potassium channel openers (retigabine and ezogabine) for *KCNQ2* DEE, a powerful highly selective $Na_v1.6$ inhibitor for *SCN8A* DEE[186], and a selective GluN2B-negative allosteric modulator (radiprodil) for *GRIN2B* GOF DEE[187].

With recent scientific insights into the marked genetic heterogeneity and phenotype–genotype complexity of DEEs, it is unsurprising that few evidence-based trials to guide therapy currently exist. However, several trials have focused on orphan genetic DEEs, such as Dravet syndrome and *CDKL5* deficiency disorder. Randomized placebo-controlled trials (RCTs) of cannabidiol demonstrated efficacy in Dravet syndrome, LGS and TSC, with significant median percentage reductions in target seizures compared with placebo of 38.9%[188], 41.9%[189] and 48.6%[190], respectively. However, a statistically significant reduction in seizures is not as important as complete seizure control in terms of improving a patient's quality of life. A phase II RCT of soticlestat in patients with Dravet syndrome showed a significant placebo-adjusted median reduction in convulsive seizure frequency of 46% over the full treatment period, whereas reduction in drop seizures in those with LGS was not significant[188,191]. A RCT in *CDKL5* deficiency disorder found a median percentage change in 28-day major motor seizure frequency of −30.7% with ganaxolone, compared with −6.9% for placebo. Treatment-emergent adverse events occurred in 43 of 50 patients (86%) in the ganaxolone group and in 45 of 51 patients (88%) in the placebo group[192].

Other controlled trials have been designed based on clinical experience suggesting efficacy in specific DEEs. In Dravet syndrome, a RCT of stiripentol demonstrated clear efficacy[193], after initially being trialled in drug-resistant epilepsy. Stiripentol was more effective, in association with clobazam, in individuals with Dravet syndrome[194]. In a RCT of stable doses of clobazam and valproate, 71% of children with Dravet syndrome receiving add-on stiripentol achieved a reduction in seizures of >50% compared with only 5% of those receiving placebo[193]. Owing to the trial design, one cannot infer that this combination of ASMs is necessarily the most effective; real-world data may show other combinations to be more effective or have improved tolerability.

Identification of the efficacy of fenfluramine in Dravet syndrome followed the observation that it is particularly beneficial in children with drug-resistant, self-induced photosensitive epilepsy[195]; fenfluramine resulted in seizure freedom in 7 of 12 patients with Dravet syndrome in one study[196]. In the first of two RCTs, fenfluramine at two different doses was added to antiseizure regimens without stiripentol[197]. The higher dose of fenfluramine was associated with a significantly greater likelihood of achieving a reduction of >50% (68% higher dose versus 12% placebo) and a reduction of >75% ; (50% higher dose versus 2% placebo) in convulsive seizure frequency. In the second RCT, an intermediate dose of fenfluramine, owing to drug interactions, was added to stiripentol and resulted in a reduction of >50% (54% vs 5% placebo) and a reduction of >75% (35% vs 2% placebo) in convulsive seizures[198]. Subsequent studies of fenfluramine in Dravet syndrome demonstrated dose-dependent clinically meaningful

effects in regulating behaviour, emotion, cognition and everyday executive functions in children of preschool age[199], and sustained efficacy and safety in children, adolescents and adults in real-world practice[200,201].

Fenfluramine also proved effective in reducing drop seizures in LGS in a double-blind, placebo-controlled, parallel-group RCT[202]. The most responsive seizure type was the GTCS in 120 of 263 patients (46%), with a decrease in frequency of 45.7% and 58.2% in the higher and lower dose groups, respectively. The most common treatment-emergent adverse events included decreased appetite (22%), somnolence (13%) and fatigue (13%). The open-label extension phase of this study, in which 142 patients completed their final visit after 12 months[203], confirmed GTCS to be the most responsive seizure type, with median reductions over the entire extension period of 48.8%, whereas tonic seizures reduced by 35.8%.

Of note, interest is growing in clinical trials of new or repurposed drugs that target orphan syndromes or gene-specific DEEs. These may target the altered neurobiological pathways even though the underlying epileptogenic mechanisms often remain unclear. One example is the EXIST-3 RCT in which the effectiveness of the mTOR inhibitor everolimus was investigated in patients with drug-resistant focal seizures in the setting of TSC, due to pathogenic variants in the mTOR pathway genes, *TSC1* or *TSC2*. In this RCT, responder rates were greater with higher-dose everolimus than with placebo; however, they were perhaps less compelling than might have been expected for a precision therapy (40% vs 15.1%; $P < 0.0001$)[131]. Effects on cognition and other neuropsychiatric symptoms were not reported. In contrast to most RCTs, the clinical response increased over time as measured in the open-label extension study in patients on everolimus for ≥48 weeks, and was postulated to be due to a disease-modifying effect[204]. A post hoc analysis of patients <18 years showed that children <6 years of age had greater benefit, suggesting that this precision therapy may be more beneficial if commenced earlier[205]. In addition to the efforts devoted to development of precision therapies targeting aetiologies, RCTs of new or repurposed agents for epilepsy syndromes also hold promise. Epilepsy syndromes remain clinically important, as consistent phenotypes may suggest pathways modifiable by more broadly beneficial ASMs, and may prove to be more pharmacoeconomically viable than drugs targeting each genetic disease[4].

Avoiding factors that cause seizure exacerbation

Environmental factors exacerbate seizures in many patients with a DEE. In Dravet syndrome and *PCDH19* clustering epilepsies, fever or hyperthermia (even simply a hot environment or hot bath) are well-recognized seizure triggers, and may have even more serious consequences. For instance, a 10-year-old girl with Dravet syndrome, who had been seizure-free for 2 years, died as a result of walking outside on an extremely hot day (46.5 °C)[206]. Fatigue, stress or excitement in most patients, and environmental photic or pattern stimulation in some, may trigger seizures. The precipitating role of such factors varies between patients, and should be carefully extracted from their disease history. Instructions to avoid precipitants (or to use rescue medication when appropriate) should be provided to families.

Certain ASMs may lead to seizure exacerbation in specific genetic DEEs. For example, in Dravet syndrome, SCBs such as carbamazepine and oxcarbazepine should be avoided[207]. However, the SCB topiramate can be useful in Dravet syndrome[181], whereas others, such as lamotrigine and phenytoin, may exacerbate seizures in some patients and be helpful in others[208,209].

Treatment of acute seizures and status epilepticus

Episodes of repetitive seizures or status epilepticus often occur in patients with a DEE. Care-givers of every individual with a DEE who has experienced repetitive seizures or status epilepticus should have a seizure action plan for first aid and out-of-hospital rescue therapy. Different genetic DEEs have different risks of convulsive and non-convulsive status epilepticus and death[19]; understanding these risks informs diagnosis, prognostic counselling and management strategies. These include recognition and treatment of precipitating factors (for example, prompt treatment of fever). Early, appropriate treatment of seizures may reduce the likelihood of status epilepticus[210]. Guidance for in-hospital acute seizure management should also be provided, although different hospitals have their own status epilepticus protocols. This is a delicate matter, as simply adopting a protocol reduces mortality and morbidity, although there is little evidence to show that any one of the numerous recommended protocols is better than another[211]. Furthermore, intensive care specialists may be reluctant to use a protocol with which they are unfamiliar.

The main options for out-of-hospital intervention include benzodiazepines such as midazolam (nasal or buccal), diazepam (nasal, rectal or buccal), lorazepam (buccal or sublingual) or clonazepam (oral)[212]. Pre-hospital benzodiazepine administration may be effective in controlling repetitive seizures or status epilepticus and may avoid hospitalization[212,213]. Overdosing should be avoided due to the increased risk of respiratory depression[214].

Targeting comorbidities

The severity of epilepsy in patients with a DEE should not reduce the focus on comorbidities, as cognitive disorders, psychiatric disorders (such as ASD, anxiety, mood and behavioural disorders, and psychosis), and motor and medical disorders occur frequently[110,152,153,156,215]. The aetiologies are multifactorial, reflecting the underlying neurobiology of the DEE, which is exacerbated by poorly controlled seizures, frequent epileptiform activity on EEG, sedative and psychiatric adverse effects of medication, restrictions and social stigma[216]. Patients with a DEE are at high risk of the typical medical complications associated with severe neurodevelopmental impairment, including aspiration pneumonia, feeding problems, constipation, sleep disorders and orthopaedic deformities[110,152,215]. A multidisciplinary team is essential to address the care of these severely disabled patients.

In patients with severe behavioural disorders, a trial of pharmacological treatment such as risperidone, aripiprazole or a selective serotonin reuptake inhibitor may be warranted, with careful discussion about potential adverse effects, including sedation, weight gain and serotonin syndrome, and the risk of seizure exacerbation. Forced normalization, in which psychiatric problems emerge in the setting of seizure control, can occur in patients with longstanding drug-resistant seizures[217].

Quality of life

Health-related quality of life (HRQOL) studies measure the effect of chronic disease on an individual's physical, social and mental well-being[218]. In children with a DEE, quality of life measures extend to parents, carers and the wider family, as there is lifelong care-giver responsibility and burden. Such measures address important personal, societal and health economic consequences of disease.

Classification of DEEs into syndromes has enabled condition-specific patient advocacy groups to form, facilitating research participation of carers[215,219]. Care-givers emphasize the importance of

sleep, communication, behaviour, daily activities, motor skills and language problems, which often eclipse seizures in importance as the child ages[219]. Given the young age at presentation, intellectual disability and comorbidities in patients with a DEE, HRQOL assessments comprise proxy questionnaires completed by care-givers. Studies typically incorporate several validated questionnaires to assess different aspects of HRQOL, such as the Epilepsy and Learning Disability Quality of Life Questionnaire[220], the Impact of Pediatric Epilepsy Scale[221], the Pediatric Quality of Life Inventory[222], the Parenting Stress Index[223] and the Strengths and Difficulties Questionnaire[224]. By comparing phenotypic features, such as seizure type and frequency with HRQOL, studies identify predictors of outcome. RCTs now include parental questionnaires measuring behaviour and everyday function, which typically aid the descriptive aspects of the study rather than acting as primary or secondary end points[199]. The development of composite end points for DEE trials, acknowledging the importance of improving comorbidities as well as reducing seizure frequency, is a new area of trial design[225].

Cross-sectional studies in DEEs demonstrate considerably worse HRQOL than in both the general population and unselected childhood epilepsy cohorts[226]. In patients with Dravet syndrome, increased epilepsy severity and behavioural factors were strong predictors of HRQOL at baseline and at 10 years[227]. The use of SCBs leading to increased seizure frequency was associated with a reduced HRQOL at 10 years ($F(1,34) = 4.13$; $P = 0.05$)[227]. Carers of children with Dravet syndrome have more depressive symptoms than carers of patients with other drug-resistant epilepsies or in seizure remission, and are more likely to resign from employment resulting in greater financial burden on the care-giver's family[228]. Most of the burden falls on female carers. Parents of children with LGS, the vast majority mothers, reported constant anxiety, difficulties in accessing child care, restriction of social life and poor mental health[229,230].

Transition to adult care is a particularly stressful and anxiety-provoking period for care-givers. In people with TSC who developed epilepsy during childhood, 75% felt the disease led to isolation and social withdrawal and negatively affected relationships, and only 15% of respondents were optimistic about their state of health over the next 5 years[231]. Although 90% of adults with TSC remained on anti-seizure medication, almost 40% did not have neurological follow-up[231], highlighting the need for a supportive medical framework into adult life, when new medical issues often emerge[232].

Outlook

Although DEEs have a vast array of mainly genetic aetiologies that alter different developmental processes and aspects of neural cell functioning, a shared consequence is impairment of higher cortical functions, in addition to drug-resistant seizures. Although severity varies across and within specific epilepsy syndromes and genetic diseases, language, memory, attention and executive functions are usually impaired in the long term, with almost all patients having cognitive impairment, and many have features of ASD. There has been increasing awareness that ASMs that mitigate epileptic activity do not adequately address the widespread cortical dysfunction resulting from defective developmental processes and severe epilepsy. This has prompted efforts to repurpose drugs and develop new molecules and precision treatment approaches, embracing a broader therapeutic goal of curing not just the seizure disorder, but all the comorbidities.

The promise of gene therapy is both tantalizing and imminent; however, many limitations exist regarding implementation in children and adults with a DEE[233]. Many genes causing DEEs have a role in transcriptional regulation and control a range of downstream pathways that cannot be targeted individually. Dosing is an important issue, which requires a delicate balance to ensure that a GOF phenotype is not turned into a LOF phenotype, as many genes demonstrate severe phenotypes with both types of dysfunction[34]. Furthermore, the optimal timing of gene therapy administration is unclear. DEEs have, by definition, developmental effects, which are unlikely to be reversed postnatally; this limitation is likely to apply to developmental genes, receptors and channels. Thus, even early postnatal delivery of gene therapy is probably too late to fully reverse the formation of abnormal brain networks. That said, the widespread nature of neuronal dysfunction typical of DEE requires a delivery system capable of targeting the whole brain in a critical period before mature connections are in place. Mosaicism and X-linked disorders further complicate cellular targeting.

The recent advent of many forms of gene therapy is promising. Viral vectors, such as adeno-associated virus 9, enable widespread gene transfer in the adult brain[234]. However, they can only carry a limited amount of DNA, and some genes, such as *SCN1A*, remain too large for present vectors. New approaches include targeting regulatory elements of large genes, such as *SCN1A*, employing cell-selective specificity[235]. An alternative to DNA is to target mRNA using antisense oligonucleotides, which can be administered intrathecally to either inhibit or increase mRNA transcription, alter mRNA splicing or increase mRNA degradation[236]. Trials of antisense oligonucleotides in mouse models of DEEs have shown positive effects for several genes including *SCN1A*, *SCN2A*, *SCN8A* and *KCNT1* (refs. 237,238). The use of antisense oligonucleotides to increase the production of translated mRNA, termed targeted augmentation of nuclear gene output (TANGO), has been used successfully in an animal model of Dravet syndrome to increase the production of sodium channels[239], and is currently undergoing clinical trials in patients with Dravet syndrome[240]. Another approach, used to correct nonsense point mutations, has taken advantage of small molecules that induce translational readthrough, suppressing stop codons. A clinical trial is ongoing in patients with Dravet syndrome and *CDKL5* deficiency disorder[241].

There is growing interest in delineating the natural history of DEEs, often focused on paediatric studies[242]. The disease-modifying potential of new treatments, especially precision and gene therapies, can only be determined if natural history profiles of each genetic DEE are well described[243]. For most DEEs, it is not known, for example, whether and how the cognitive outcome would improve if seizures were controlled soon after epilepsy onset. It is also unclear whether differences in severity of cognitive impairment among family members with the same *SCN1A* pathogenic variant, where one individual has Dravet syndrome and another has GEFS+, are due to genomic background, environmental factors or more severe seizures in the individual with Dravet syndrome[244]. Answering these questions will benefit in the future from sophisticated genomics studies and increasing involvement of family associations[215,245]. These associations focus on advocacy and fundraising for research on their specific genetic DEE, for which, because of their rarity, adequate attention and development of precision therapies would otherwise be delayed for years.

Despite these caveats, the future is far brighter for patients with a DEE than ever before. In just 23 years, the field has moved from considering that DEEs are acquired disorders to identifying the genetic aetiology underlying DEEs in at least 50% of patients. Development of new genomic methodologies will probably discover the aetiology in the remaining individuals. Already, techniques are emerging, such as

polygenic risk scores, that aid in understanding the interaction of rare and common variations in determining phenotypic variability[244,246]. In the future, exploration of environmental factors, such as viral infections, is likely to illuminate phenotypic differences further. Development of precision therapies, in their many guises, will hopefully lead to dramatic improvements in the outcome for patients with a DEE with the ultimate expectation, one day, of cure.

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